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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/684,554	10/06/2000	John F. Engelhardt	875.024US1	4157

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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

EXAMINER	
WINKLER, ULRIKE	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/19/2004 19

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/684,554	ENGELHARDT ET AL.	
	Examiner	Art Unit	
	Ulrike Winkler	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 August 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8-11,19-21,23-37,41-43 and 46-58* is/are pending in the application.

4a) Of the above claim(s) *2-4,8,10,11,21,23-37,41-43 and 48-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,9,19,20,46,47 and 55-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *16*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed August 13, 2003 (Paper No. 18) in response to the Office Action of March 11, 2003 and the Interview of June 23, 2003 is acknowledged and has been entered. Claims 5-7, 12-18, 22, 38-40 and 44-45 have been cancelled. Claims 55-58 have been added, please note in the response filed August 13, 2003, claim 57 appears as a duplicate.

Newly amended claims 4, 10 and 11 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The claims are now drawn to enhancers which were grouped in Group III of the Election/Restriction requirement of Paper No. 8 mailed August 26, 2002. Applicants have indicated that the amendments are supported in the specification on page 10, lines 9-20, the specification talks about using an enhancer in the AAV constructs.

Since applicant has received an action on the merits for the originally presented invention Group II drawn to promoters, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 4 and 10 are withdrawn form consideration as being drawn to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Again, applicant is reminded that claim 1 is a linking claim.

Therefore, claims 1, 9, 19, 20, 46, 47 and 55-58 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Information Disclosure Statement

An initialed and dated copy of Applicant's supplemental IDS form 1449, Paper No. 16, is attached to the instant Office Action.

Drawings

The office acknowledges the receipt of the new drawing.

Claim Rejections - 35 USC § 102

The rejection of claims 4, 10 and 11 under 35 U.S.C. 102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) **is withdrawn** in view of Applicant's amendments to the claims which indicate that the *cis*-acting transcription regulatory elements are not promoters the claims are interpreted to read on enhancers which are grouped with Group III.

The rejection of claims 1, 9, 46 and 47 and newly added claims 55 and 56 under 35 U.S.C. 102(e) as being anticipated by Engelhardt et al. (U.S. Pat. No. 6,436,392 B1) **is maintained** for reasons of record.

Applicant's amendments and arguments directed to the newly amended claims have been fully considered but fail to persuade. Applicants have amended claims 1 and 19 to comprise at least one "*cis*-acting heterologous transcriptional regulatory element". Applicant arguments are that the "*cis*-acting heterologous transcriptional regulatory element" must "function in a host cell". Applicants argue that the cited art does not teach this. It appears that Applicant's are attributing a special meaning to "*cis*-acting heterologous transcriptional regulatory element" and to "functional in a host cell" that has not been defined in the specification. The specification in

example 1, figures 1, 14A and 24B indicate that CMV promoter function as the *cis*-acting heterologous transcriptional regulatory element.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

This provisional rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the copending application was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131. This rejection may not be overcome by the filing of a terminal disclaimer. See *In re Bartfeld*, 925 F.2d 1450, 17 USPQ2d 1885 (Fed. Cir. 1991).

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 9, 11, 46 and 47).

The host cells of the patented methods comprises at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). The second DNA comprising a portion of an open reading frame operably linked to a promoter (see

claim 9 and figure 14A, column 3, lines 20-42). Therefore, the instant invention is anticipated by Engelhardt et al.

The rejection of claims 4, 10 and 11 under 35 U.S.C. 102(e) as being anticipated by Couto et al. (U.S. Pat. No. 6, 200,560) or Couto et al. (U.S. Pat. No. 6, 221, 349) **is withdrawn** in view of Applicant's amendments to the claims which indicate that the *cis*-acting transcription regulatory elements are not promoters the claims are interpreted to read on enhancers which are grouped with Group III.

The rejection of claims 1, 9, 46, 47 and newly added claims 55 and 56 under 35 U.S.C. 102(e) as being anticipated by Couto et al. (U.S. Pat. No. 6, 200,560) or Couto et al. (U.S. Pat. No. 6, 221, 349) **is maintained** for reasons of record.

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claim 1). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 9, 46 and 47).

The references disclose the introduction of two recombinant AAV virus vectors into a cell for the production of factor VIII (see examples 1, 11, see figure 7). These vectors are capable of delivering nucleic acid containing constructs which result in the production of full-length therapeutic levels of biologically active Factor VIII in the recipient individual *in vivo*. The heavy and light chains of human Factor VIII (hFVIII) were assembled and cloned as expression cassettes into AAV vectors. Both vectors contain the promoter and the first non-coding intron (from -573 to +985) from the human elongation factor 1.alpha. (EF1.alpha.) gene (EF1alpha

promoter and first intron). Each vector also contains the first 57 base pairs of the FVIII heavy chain encoding the 19 amino acid signal sequence. The heavy chain construct encodes the A1 and A2 domains and 5 amino acids from the N terminus of the B domain. The light chain vector encodes 85 amino acids of the carboxy terminal B domain, in addition to the A3, C1, and C2 domains. Both vectors utilize the human growth hormone (hGfl) polyadenylation signal. The expression cassettes were inserted between AAV ITRs. The transcription of both vectors was assayed (see examples 12) in the liver of mice. Therefore, the instant invention is anticipated by Couto et al.

The rejection of claims 4, 10 and 11 under 35 U.S.C. 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology 1998) **is withdrawn** in view of Applicant's amendments to the claims which indicate that the *cis*-acting transcription regulatory elements are not promoters the claims are interpreted to read on enhancers which are grouped with Group III.

The rejection claims 1, 9, 19, 20, 46 and 47 and newly added claims 55, 56 and 58 are rejected under 35 U.S.C. 102(b) as being anticipated by Rendahl et al. (Nature Biotechnology 1998) **is maintained** for reasons of record.

The instant invention is drawn to a composition comprising two recombinant adenovirus vectors. The composition requires two recombinant AAV constructs that comprise a 5'and 3' ITR with a heterologous DNA sequence in between (claims 1 and 19). The vectors comprise a promoter (a heterologous transcriptional element) linked to the open reading frame (claims 4, 9, 11, 19, 46 and 47). The cis-acting heterologous transcriptional regulatory element of one rAAV is functional in the host cell, which vector regulates the expression of another therapeutic gene

(claim 19). The functional limitation (claim 19) only requires that the vector comprises sequences that can regulate another gene sequence.

Rehndahl et al. disclose the *in vivo* regulation of gene expression following co-injection of two separate recombinant adeno-associated virus vectors, one encoding an inducible murine erythropoietin transgene (a therapeutic gene) and the other a transcriptional activator, directly into the skeletal muscle of adult immunocompetent mice. Construct one (rAAV-CMV-tTA) comprises the tetracylince responsive transactivator and the mouse protamine polyadenylation site. Vector two (rAAV-(tetO)7-minCMV-mEPO) tetracycline responsive element reiterated 7 times regulating the minimal CMV promoter bovine growth hormone polyadenylation site. In this instance the expression tTA from one AAV construct regulates the expression of the inducible murine erythropoietin transgene which is found on the other AAV construct. The CMV promoter is functional in a host cell. The vectors are shown to be expressed in the same cells indicating that these cells comprise both AAV constructs. Therefore, the instant invention is anticipated by Rendahl et al.

Double Patenting

The rejection of claims 4, 10 and 11 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292 **is withdrawn** in view of Applicant's amendments to the claims which indicate that the *cis*-acting transcription regulatory elements are not promoters the claims are interpreted to read on enhancers which are grouped with Group III.

The rejection of claims 1, 9, 46 and 47 and newly added claims 55 and 56 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8-15 of U.S. Patent No. 6,436,292 **is maintained** for reasons of record. The host cells of the patented methods comprises at least two recombinant AAV vectors each comprises a 5' and 3' LTR, a heterologous DNA segment (open reading frame). Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention does not exclude the compositions used in the patented methods.

New rejection in view of Applicant's amendments:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 57 and 58 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are directed to a combination of AAV vectors that do not contain a heterologous splice site. It is not clear were in the specification there is support for using a combination of vectors in which both vectors do not contain a heterologous splice site.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached at 571-272-0902.

The official fax phone number for the organization where this application or proceeding is assigned is 703-872-9306; for informal communications please the fax phone number is 571-273-0912.

ULRIKE WINKLER, PHD.
PATENT EXAMINER 4/16/04